

# Local Hemodynamic Forces After Stenting: Implications on Restenosis and Thrombosis

Jaryl Ng<sup>1</sup>; Christos V. Bourantas<sup>2,3</sup>; Ryo Torii<sup>4</sup>; Ang Hui Ying<sup>1</sup>; Erhan Tenekecioglu<sup>5</sup>; Patrick W. Serruys<sup>5,6</sup>; Nicolas Foin<sup>1,7\*</sup>

## Affiliations:

1. National Heart Centre Singapore, Singapore
2. Department of Cardiovascular Sciences, University College London, London, United Kingdom
3. Department of Cardiology, Barts Health NHS Trust, London, United Kingdom
4. Department of Mechanical Engineering, University College London, London, United Kingdom
5. Thoraxcenter, Erasmus MC, Rotterdam Erasmus University, Netherlands
6. National Heart & Lung Institute, Imperial College London, United Kingdom
7. Duke-NUS Medical School, National University of Singapore, Singapore

\* Corresponding author

Adj. A/Prof. Nicolas Foin, PhD

National Heart Research Institute Singapore

5 Hospital Drive, Singapore 169609

Email: Nicolas.foin@gmail.com

## Highlights

- Stent restenosis and thrombosis are major complications that can develop after percutaneous coronary intervention and are associated with risks of reintervention and potential acute coronary events.
- Hemodynamic forces trigger biological pathways that are involved in both stent thrombosis and restenosis.
- Effort should be made to design drug-eluting stents and bioresorbable scaffolds that will have an optimal hemodynamic profile so as to improve their safety and reduce the incidence of stent/scaffold related adverse events.
- Optimal stent/scaffold expansion is associated with improved local hemodynamics and low incidence of adverse events.

## **Abstract**

Local hemodynamic forces are well-known to modulate atherosclerotic evolution, which remains one of the largest cause of death worldwide. Percutaneous coronary interventions with stent implantation restores blood flow to the downstream myocardium and is only limited by stent failure caused by restenosis, stent thrombosis, or neoatherosclerosis. Cumulative evidence has shown that local hemodynamic forces affect restenosis and the platelet activation process, modulating the pathophysiological mechanisms that lead to stent failure. This article first covers the pathophysiological mechanisms through which wall shear stress regulates arterial disease formation/neointima proliferation and the role of shear rate on stent thrombosis. Subsequently, the article reviews the current evidence on (1) the implications of stent design on the local hemodynamic forces, and (2) how stent/scaffold expansion can influence local flow, thereby affecting the risk of adverse events.

**Key Words:** hemodynamics, percutaneous coronary intervention, stents, thrombosis

## **List of Abbreviations**

PCI Percutaneous Coronary Intervention  
3D Three-Dimensional  
OCT Optical Coherence Tomography  
IVUS Intravascular Ultrasound  
ESS Endothelial Shear Stress  
CFD Computational Fluid Dynamics  
BMS Bare Metal Stent  
DES Drug Eluting Stent  
BVS Bioresorbable Vascular Scaffold  
vWF Von Willebrand Factor  
BRS Bioresorbable Scaffold  
MLD Minimum Lumen Diameter  
DoCE Device Orientated Composite Endpoint  
ISA Incomplete Strut Apposition

## Introduction

Advances in stent technology, drug polymer biocompatibility, and design have improved the safety and efficacy of coronary stent devices. Despite these advances, restenosis and device thrombosis remain a major concern and are still affecting longterm clinical outcomes.<sup>1</sup> Randomized trials and clinical registries show that the rate of stent thrombosis is <1% after 1 year, and the restenosis rates remain at ≈5%.<sup>2</sup> Nevertheless, the cumulative incidences of these events in the long term still remain substantial. Hence, it is crucial to identify the causes of stent/scaffold failure and understand how the hemodynamic environment impacts clinical outcomes postpercutaneous coronary intervention (PCI). With current high-resolution intravascular imaging, geometrically accurate representation of patient-specific coronary anatomy can be reconstructed for blood flow simulation, enabling precise endothelial shear stress (ESS) maps to be generated (Figure 1). Patient-specific biomechanical forces can then be quantified to investigate the pathophysiological implications of the flow patterns in stented/scaffolded segments and their role in neointimal hyperplasia and device thrombosis.<sup>4</sup> This article will first define the metrics of local hemodynamics and introduce the main pathophysiological mechanisms, followed by a summary on the evidence about the role of the local hemodynamics on stent thrombosis and restenosis.

### Metrics of Local Hemodynamics

#### Shear Rate

Shear rate is defined as the local velocity gradient between adjacent blood flow streamlines (Figure 2) and provides a quantitative representation of local flow disturbance. Shear rate is also one of the main regulators of platelet activation and thrombosis.<sup>6,7</sup> In medium- to large-sized arteries, physiological shear rate falls within the range of 100 to 1000 s<sup>-1</sup>.<sup>8</sup> In silico and in vivo studies have shown that in stented/scaffolded segments, the rigid protruding and malapposed struts create flow obstructions that disrupt blood flow, resulting in flow separation and shear rates >2000 s<sup>-1</sup>.<sup>9-12</sup>

#### Endothelial Shear Stress

ESS is estimated by multiplying the shear rate at the wall surface with the viscosity of blood (Figure 2) and represents the tangential frictional stress on the vessel wall imposed by the flowing blood. In vivo evaluations of ESS using computational fluid dynamic methods have shown that its distribution predicts atherosclerotic lesion development.<sup>13-17</sup> Low and oscillatory ESS is a known modulator of arterial wall physiology, specifically via impaired endothelial cell function where low ESS has been shown to regulate gene expression and vascular proinflammatory response through multiple mechanotransduction pathways.<sup>18,19</sup>

## Hemodynamics Impact on Disease Process

### Low ESS and Arterial Disease Development

The endothelium senses changes in ESS via several mechanotransduction processes that involve activation/release of signalling proteins in endothelial cells and smooth muscle cells, which in turn regulate vessel wall physiology.<sup>20-25</sup> The type and magnitude of response are determined by the magnitude and direction of ESS.<sup>26</sup> Experimental studies have demonstrated that low ESS (<10 dynes/cm<sup>2</sup>) causes misalignment of the endothelium<sup>27,28</sup> and disruption of cell-cell junctions.<sup>29-31</sup> This increases the permeability of the endothelium to circulating lipids and inflammatory regulators.<sup>32-34</sup> In addition, low ESS decreases vasodilator,<sup>25</sup> fibrinolytics,<sup>35</sup> and antioxidants<sup>36</sup> and increases expression of cell adhesion molecules,<sup>22</sup> growth factors,<sup>37</sup>

vasoconstrictors,<sup>38</sup> oxidative species,<sup>39</sup> proteolytic enzymes,<sup>40</sup> and acute inflammatory mediators.<sup>41</sup> This leads to endothelial dysfunction, vessel inflammation, and smooth muscle cells proliferation, contributing to plaque growth and arterial expansive remodeling.<sup>14</sup> The behavior of smooth muscle cells is regulated by the interaction with endothelial cells but also by mechanical forces, such as shear stress. ESS leads to the release of platelet-driven growth factor and transforming growth factor which causes smooth muscle cell proliferation and migration, subsequently resulting in neointimal hyperplasia and restenosis.<sup>14,26,38</sup> When there is no endothelium, Liu and Goldman<sup>42</sup> demonstrated that smooth muscle cell migration is significantly suppressed under laminar flow conditions compared with regions that are exposed to recirculating and unsteady flow.

Shear modification has been shown to modulate plaque progression and the degree of inflammation in animal models.<sup>18,43</sup> Low and oscillating ESS has been reported to accelerate vulnerable atherosclerotic plaque formation.<sup>18,19</sup> In a recent experimental study using intracoronary shear-modifying stents in hypercholesterolemic pigs, Pedrigi et al<sup>44</sup> reported an  $\approx 3$ - fold increase in plaque burden distal to the shear-modifying stents compared with both proximal segment and the control arteries. Advanced coronary plaques were collocated mostly downstream of the shear-modifying stents, in regions of low ESS.<sup>44</sup> Although low ESS alone has been shown to increase plaque progression, a combination of low and oscillatory ESS is considered to be particularly atherogenic. Flow simulations on intravascular ultrasound–derived vessels of patients with coronary artery disease demonstrated that low and oscillatory ESS can cause plaques to evolve into a more vulnerable phenotype compared with low ESS only because of more inflammation and necrotic core progression.<sup>45</sup>

The Table summarizes studies that have examined the impact of low ESS on atherosclerosis and restenosis. Most studies associated regions of low ESS with increased plaque burden or atherosclerosis plaque progression.

### **Low ESS and Restenosis Post-PCI**

Studies have reported that there is also an inverse correlation between baseline ESS and neointimal thickness at follow-up (ie, low ESS increases neointimal proliferation). In the study conducted by Wentzel et al,<sup>50</sup> blood flow simulation was performed in segments implanted with bare metal stents (BMS). The ESS distribution was estimated on the reconstructed surfaces of stented vessel segments after implantation and at 6-month follow-up. An inverse association was found between baseline ESS and neointima formation at 6-month follow-up.<sup>50</sup> These findings were confirmed in several other studies.<sup>3,50,52,53,58,59</sup> Papafaklis et al<sup>53</sup> investigated the implications of the local hemodynamic forces on neointimal response in BMS and first-generation drug-eluting stents (DES). The study reported an inverse correlation between ESS and neointima response in BMS while in DES vessels, wall response was shown to depend on the antiproliferative drug. Sirolimus seems to reduce the amount of positive cell cycle regulators and increase the amount of cell cycle inhibitors, leading to inhibited cell migration, proliferation, and desensitization of the cells to the effects of low ESS.

The PREDICTION study (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology) was the largest ESS study investigating the implications of the local hemodynamic forces on the healing response after BMS and first-generation DES in vivo. The relationship between postprocedural ESS and neointimal in-stent hyperplasia was investigated by comparing the 3-dimensional reconstructed stented segments of 374 patients at baseline immediately after stent implantation and 6- to 10-month follow-up.<sup>17,57</sup> The study demonstrated an inverse relationship between ESS and neointima response in BMS while in DES, the neointima tissue was too limited for assessment of the association between ESS and neointima tissue.<sup>57</sup> Bourantas et al<sup>56</sup> have also investigated the association between ESS and neointima proliferation using serial intravascular ultrasound imaging in 43 patients

implanted with either BMS or biolimus-eluting stents at baseline and 13-month follow-up. Negative correlations were noted between ESS and neointima thickness in both groups. There was also a negative correlation between ESS and the percentage of neointimal necrotic core component ( $P=0.015$ ) in BMS while the limited neointima formation impeded the evaluation of the effect of ESS on neointima characteristics in DES.

Optical coherence tomography–based reconstruction was used to assess the implications of the ESS on neointima response in 12 patients implanted with an everolimus-eluting bioresorbable vascular scaffold (BVS; Absorb BVS; Abbott Vascular, Santa Clara, CA). In this analysis, the optical coherence tomography data acquired at baseline and 1-year follow-up were used to model vessel geometry.<sup>55</sup> The authors showed that the protruding struts resulted in low ESS in the areas between the struts and high ESS at the top of the struts. A strong negative correlation was observed between baseline ESS and neointimal thickness at follow-up; and increased neointima proliferation was found in the areas between the struts where the ESS was. This resulted in a smoothing of the rugged luminal surface and a homogenization of the ESS at 2-year follow-up.<sup>55</sup>

Recently, Torii et al<sup>60</sup> evaluated the implications of the local flow patterns on neoatherosclerotic lesion formation in 35 patients implanted with either BMS or DES. The patients were admitted with coronary events attributed to stent failure and had neoatherosclerotic lesions based on optical coherence tomography images. An inverse association was noted between ESS and the incidence and burden of lipid-rich neoatherosclerotic tissue ( $P<0.001$ ). Segments exposed to low ESS ( $<1$  Pa) were more likely to exhibit macrophage accumulations, thrombus, or neointima discontinuities compared with those exposed to normal or high ESS ( $P<0.001$ ). These results indicate that local ESS also plays a role in the regulation of neoatherosclerosis lesion formation in stented segments<sup>60</sup> (Figure 3).

### **Shear Rate Modulation of Platelet Activation and Thrombosis**

Shear rate seems to play an important role on vessel physiology and determines the concentration of platelets and adhesion proteins near the vessel wall. In segments exposed to high shear rate, red blood cells cause platelets displacement toward the vessel wall via a process called margination. The accumulation of platelets and adhesion proteins near the vessel wall creates a prothrombotic environment.<sup>61–63</sup>

When adhesion proteins like Von Willebrand factor and fibrinogen come in contact with a thrombogenic surface (ie, ruptured plaques and stent struts), a clot cascade is triggered. Once the adhesion proteins attach to the thrombogenic surface, they stimulate activated platelets to bind to the surface. At high shear rates, the globular structure of the Von Willebrand factor elongates into a string structure,<sup>64–67</sup> increasing the amount of platelet binding sites on the molecule. With high shear rates ( $\approx 10\,000\text{ s}^{-1}$ ), Von Willebrand factor strings combine to form nets that further increase the amount of platelet binding sites by  $\approx 10\,000\times$ .<sup>66,68</sup> The attracted platelets are exposed to high ESS, which shortens their activation time.<sup>69</sup> As the thrombus grows, more Von Willebrand factor nets are formed which subsequently increase the number of bound platelets. This positive feedback loop results in thrombus formation.<sup>69</sup>

## Stent-Induced Hemodynamic Changes During PCI

In the BMS era, excessive neointimal proliferation was a major drawback that caused early restenosis.<sup>70</sup> With the introduction of DES, the occurrence of restenosis has been significantly reduced. However, in-stent thrombosis has remained an issue observed at both short- and long-term follow-up. It was reported that strut dimensions and the distance of the struts from the vessel wall affect stent thrombogenicity more than the presence of drug coatings.<sup>11</sup> Although stent thrombosis may have a relatively low incidence (0.6%–3.4%),<sup>71</sup> it is still the most feared complication after PCI because of the associated mortality risk for the patients.<sup>72</sup> Studies have revealed that the major causes of early stent thrombosis (<30 days) are largely because of stent underexpansion and malapposition while late stent thrombosis (>30 days) is found frequently with late remodeling, stent strut malapposition, and delayed endothelial coverage.<sup>71</sup>

### Stent Design

Stent design has an impact on the flow dynamics in stented segments. Strut thickness, in particular, is a major factor affecting local shear rate and ESS post-PCI. Large strut thickness increases the amount of foreign material in the lumen and leads to flow disturbances, flow separation, and areas of recirculation zones, thereby increasing the risk of stent thrombosis.<sup>9–12,55,73</sup> Models have shown that the maximal distance between the helical rings should be at least 6× the strut thickness to recover any laminar flow in the interstrut zones.<sup>74</sup> Smaller strut thickness can improve re-endothelialization and reduce peristrut inflammation and fibrin deposition.<sup>75–77</sup> In the BMS era, clinical studies have reported improved outcomes in patients implanted with thin strut stents.<sup>78–81</sup> Flow separation distance was also found to be longer in nonstreamlined struts (rectangular) compared with streamlined struts (circular/ovoid).<sup>82</sup> Polymer coating is another essential part of stent design that can affect stent's thrombogenicity. Otsuka et al<sup>83</sup> observed in an ex vivo model that the fluoropolymer-coated Xience DES showed a significantly lower percentage of a thrombusoccupied areas compared with a DES with contemporary biodegradable coatings. Kolandaivelu et al<sup>11</sup> investigated the implications of stent design and drug coating on the incidence of stent thrombosis by deploying DES and BMS with identical design but different strut thickness in ex vivo perfusion models. Results indicated that DES with a biocompatible drug coating had a 0.65-fold lower thrombogenicity compared with BMS while thicker struts stents were 1.5× more thrombogenic than thin strut stents with the same design.<sup>11</sup>

Current bioresorbable scaffolds (BRS) have thicker struts ( $\geq 150\ \mu\text{m}$ ) compared with second-generation metallic DES ( $\leq 100\ \mu\text{m}$ ). One of the most widely examined BRS is the Abbott Vascular's Absorb BVS, which is fabricated from a poly-L-lactic acid backbone. The Absorb BVS has a strut thickness of  $156\ \mu\text{m}$  and a width of  $190\ \mu\text{m}$  while the Xience DES has a total strut thickness of  $89\ \mu\text{m}$ . Because of the lower elastic modulus and tensile strength of the bioresorbable materials, thicker struts are often required in BRS to achieve a radial force similar to that of conventional metallic platforms.<sup>84–86</sup>

Studies have shown more extensive neointimal hyperplasia and late lumen loss in BRS compared with DES at showed >50% increase in maximum shear rate values with protruding stent struts<sup>10</sup> compared with embedded struts. These flow patterns around indented struts are commonly associated with increased platelet adhesion<sup>11,93</sup> and inflammatory response,<sup>94</sup> as well as reduced re-endothelialization.<sup>75,95–97</sup> short-term follow-up.<sup>85,87–91</sup> Large strut size and other factors, such as scaffold underexpansion, incomplete scaffolding, and the acidic environment during polymer dissolution, may play a role in causing late lumen loss in BRS device. It has been hypothesized that the large strut profile of current generation of BRS is harder to embed in the tissue, hence creating a larger obstacle for blood flow.<sup>92</sup> Computational flow simulations showed >50% increase in maximum shear rate values with protruding stent struts<sup>10</sup> compared with embedded struts. These flow patterns around indented struts are commonly associated with increased platelet adhesion<sup>11,93</sup> and inflammatory response,<sup>94</sup> as well as reduced re-endothelialization.<sup>75,95–97</sup>

## Under Expansion

Stent underexpansion is usually quantified by the postprocedural diameter stenosis in quantitative coronary angiography and intravascular imaging. This is done by measuring the minimum lumen area of the stent/scaffold segment and relative percentage area stenosis. Underexpansion can be caused by inappropriate lesion preparation and postdilatation of the implanted stent/scaffold with too small balloons or insufficient pressure, particularly in fibrotic or fibrocalcific lesion types.<sup>98</sup> Stent underexpansion leads to shear stress concentration on the edges of the stent struts and higher jet and shear rate in the underexpanded segment, which may increase the risk of stent thrombosis.<sup>99</sup> Stent underexpansion has been commonly associated with early stent thrombosis (>30 days).<sup>100–102</sup> Fujii et al<sup>101</sup> conducted an analysis on 15 patients admitted for stent thrombosis and compared them with 45 matched control patients with no stent thrombosis. The study showed that the stent cross-sectional area was significantly smaller in the stent thrombosis group than in the matched control patients ( $4.3 \pm 1.6$  versus  $6.2 \pm 1.9$  mm<sup>2</sup>).<sup>101</sup>

Another study sought to compare the acute gain and late lumen loss between Absorb BVS and DES at 2-year follow-up. Thirty-three patients implanted with BVS and 26 patients implanted with the DES from the ABSORB B (ABSORB Clinical Investigation, Cohort B) and SPIRIT II (A Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System) trials were examined. Analysis showed similar acute gain (BVS:  $1.23 \pm 0.38$  mm versus DES:  $1.32 \pm 0.26$  mm;  $P=0.29$ ) and similar in device late lumen loss at 2-year follow-up (BVS:  $0.26 \pm 0.19$  mm versus DES:  $0.22 \pm 0.22$  mm;  $P=0.29$ ). However, patients implanted with BVS showed significantly lower in stent minimum lumen diameter compared with patients implanted with DES (BVS:  $2.02 \pm 0.26$  mm versus DES:  $2.22 \pm 0.34$  mm;  $P=0.01$ ).<sup>103</sup> Suwannasom et al<sup>104</sup> investigated the postprocedural asymmetry, expansion, and eccentricity indices between DES and BVS and their impact on clinical outcomes at 1-year follow-up. Pre- and postprocedural intravascular ultrasound images from 470 patients were used to calculate the asymmetry index per lesion and eccentricity index per cross-section. DES was more symmetrical and concentric compared with the BVS group post procedure, with only 8% of BVS compared with 20% of DES achieving optimal scaffold/stent expansion ( $P<0.001$ ). Although there was no difference in device-oriented composite end point at 1-year follow-up (BVS=5.2% versus DES=3.1%;  $P=0.29$ ), postprocedural device asymmetry was associated with increased event rates, with analysis showing that asymmetry index  $>0.30$  was an independent predictor of device-oriented composite end point (hazard ratio: 3.43;  $P=0.037$ ).

In a recent study, Foin et al<sup>105</sup> compared the acute expansion behavior of DES and Absorb BVS in an in vitro artery lesion model. Results showed that stent eccentricity at the minimum lumen area was lower in the BVS compared with Xience metallic stent when deployed at nominal pressure (BVS:  $0.71 \pm 0.02$  versus Xience:  $0.81 \pm 0.02$ ;  $P=0.004$ ). These anatomic differences were associated with increased shear rate and increased recirculation zones at the downstream of the underexpanded segment.<sup>105</sup> Computational fluid dynamic models have also demonstrated that even at the same diameter stenosis, an eccentric lesion induces larger recirculation. Therefore, when the stent is not symmetrically expanded, intravascular imaging should be considered to assess the final result.<sup>106</sup>

Scaffold underexpansion has been shown to be also a predictor of events in the Absorb BVS. Puricel et al<sup>84</sup> investigated the incidence, clinical and angiographic features, as well as the possible mechanisms of stent thrombosis in 1305 patients implanted with BVS. The study revealed that a low postprocedural minimum lumen diameter and low reference diameters were predictors of stent thrombosis.<sup>84</sup> The risk of stent thrombosis increased rapidly for minimum lumen diameter  $<2.4$  mm for the 2.5- to 3.0-mm BVS and  $<2.8$  mm for BVS that had a 3.5-mm diameter.<sup>84</sup> However, when aggressive lesion preparation and aggressive device postdilatation was implemented, scaffold thrombosis at 1-year follow-up fell from 3.3% to 1.0% ( $P=0.012$ ),<sup>84</sup> suggesting that the implantation technique could be the key to reducing scaffold thrombosis in BVS.

## Malapposition

Malapposition, also known as incomplete stent apposition (ISA), can affect local flow and shear profile in the stented vessel. A stent strut is considered malapposed when is not in contact with the vessel wall. Malapposed stent struts disrupt the laminar flow and can generate regions of high shear rate (Figures 4 and 5)<sup>10,11,13</sup> which are known to affect the risk of stent thrombosis.<sup>11,77,107</sup> In an in vitro experiment, Kolandaivelu et al<sup>11</sup> showed that malapposed BMS showed a 1.5-fold increase in thrombogenicity compared with wellapposed stents (P=0.001).

Malapposition also reduces stent strut coverage. A recent study analyzed the impact of baseline strut-vessel wall ISA distance on strut coverage at follow-up. As ISA increases from <100  $\mu\text{m}$  to 100 to 300  $\mu\text{m}$  and finally to >300  $\mu\text{m}$ , the percentage of uncovered struts at follow-up increased from 0% to 6.1% and 15.7%, respectively.<sup>10</sup>

Recently, reports have pointed to ISA as a possible mechanism leading to scaffold thrombosis in BRS.<sup>109–112</sup> In one study, Gomez-Lara et al showed that malapposed BRS struts are more frequently uncovered compared with apposed struts (29% of ISA struts versus 1% of apposed struts) and that intraluminal masses (possible thrombus) were seen in malapposed BRS struts more often as compared with apposed struts (39% of ISA struts versus 2% apposed struts).<sup>93,113–115</sup> Computational fluid dynamic analysis on stented/scaffolded segments demonstrated higher shear profiles in BRS compared with thin metallic DES, hence underlining the importance of imaging guidance, optimal expansion, and apposition during BRS implantation.<sup>99</sup>

## Conclusion

To summarize, suboptimal stent implantation affects the local hemodynamic forces and can lead to unfavorable clinical outcomes. Regions of low ESS after PCI are colocated with neointima and neoatherosclerosis formation. High shear gradients and flow disturbances have been shown to increase the risk of thrombosis. Therefore, effort should be made to optimize stent deployment and stent/scaffold designs to ensure an optimal hemodynamic profile and reduce the risk of complications after PCI.

## Disclosures

N. Foin holds an appointment in Philips and is adjunct faculty in National Heart Research Institute Singapore/Duke-NUS. The other authors report no conflicts.



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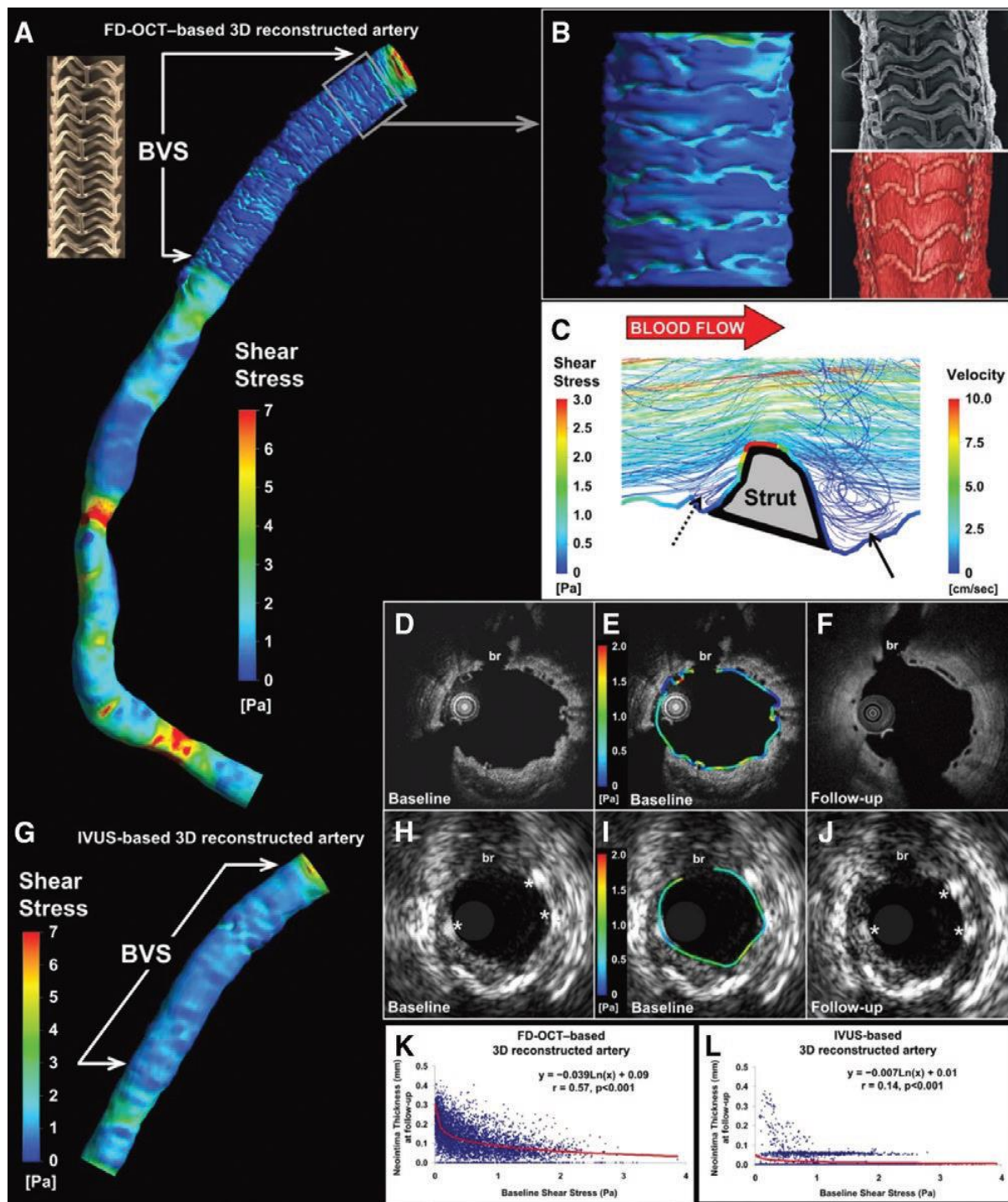
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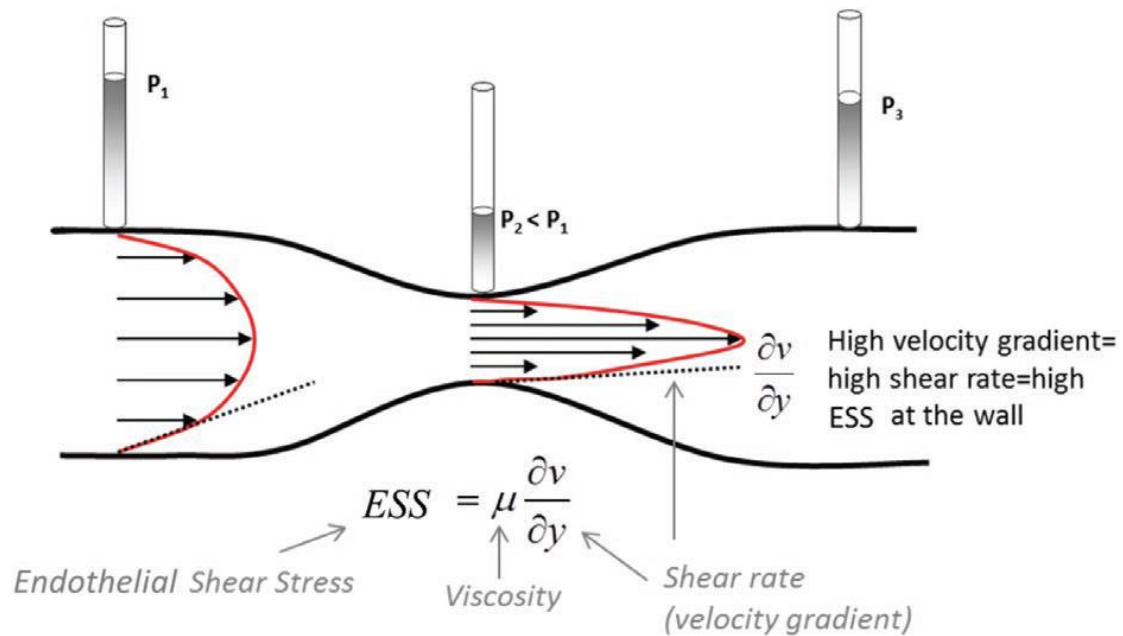
**Table 1.** Patient Studies on Atherosclerosis and Restenosis

<i>Reference</i>	<i>No. of Subjects</i>	<i>Follow-Up (mo)</i>	<i>Imaging Modality</i>	<i>Results</i>
<b>Atherosclerosis</b>				
Stone et al. (2003) <sup>15</sup>	8	6	Angiography, IVUS	Regions of low ESS showed progressive atherosclerosis and outward remodelling.
Stone et al. (2006) <sup>46</sup>	13	8±2	Angiography, IVUS	Compared to moderate/high ESS, low ESS showed plaque progression (p=0.009).
Samady et al. (2011) <sup>47</sup>	20	6	Angiography, IVUS	Regions of low ESS developed progression of plaque area (p=0.027), necrotic core (p<0.001) and decrease in vessel (p<0.001) and lumen area (p<0.001) as compared to regions of intermediate ESS. Compared to intermediate ESS, high ESS developed progression of necrotic core (p<0.001), dense calcium (p<0.001) regression of fibrous (p<0.001) and fibrofatty (p<0.001) tissue and increase in vessel (p<0.001) and lumen area (p<0.001).
Stone et al. (2012) <sup>17</sup>	506	8±2	Angiography, IVUS	Low ESS is associated with plaque enlargement and lumen narrowing, the main message being ESS is a predictor of clinical outcomes.
Vergallo et al. (2014) <sup>48</sup>	21	-	Angiography, OCT	Regions exposed to low ESS is linked to larger lipid burden (p=0.019), thinner fibrous cap (p=0.004) and higher prevalence of thin-cap fibroatheroma (p=0.037).
Hung et al. (2016) <sup>49</sup>	24	24	Angiography, IVUS	Low ESS was linked to plaque progression (p<0.0001) and constrictive remodelling (p=0.04).
<b>Restenosis</b>				
Wentzel et al. (2001) <sup>50</sup>	14	6	Angiography, IVUS	Neointimal thickness at follow up is inversely related to shear stress in BMS. Thickness = 0.59– 0.08*Shear Stress, p < 0.05.
Gijsen et al. (2003) <sup>51</sup>	6	6	Angiography, IVUS	There was a negative linear relation between neointimal thickness and shear stress. Thickness = 0.21 – 0.24*Shear Stress, R <sup>2</sup> =0.24, p < 0.001.
Papafaklis et al. (2008) <sup>52</sup>	14	6	Angiography, IVUS	In stent restenosis is inversely related to ESS after coronary with the equation: Thickness = 0.28– 0.057*Shear Stress, p<0.001. Vascular brachytherapy diminishes the inverse relationship between restenosis and ESS.
Papafaklis et al. (2010) <sup>53</sup>	30	6	IVUS	Low ESS is inversely related to neointimal thickness for both BMS (slope = -0.05mm/Pa, p = 0.001) and DES (slope = - 0.05mm/Pa, p = 0.016).
Bourantas et al. (2014) <sup>54</sup>	6	6 or 12	Angiography, OCT, IVUS	In scaffolded segments models the ESS estimated by the fusion of IVUS and X-ray angiography differs from the ESS derived from the fusion of OCT and X-ray imaging. The correlation coefficient between ESS and neointima thickness is increased in OCT based modelling comparing to IVUS based reconstructions.
Bourantas et al. (2014) <sup>55</sup>	12	12	OCT	Low ESS was associated with increased neointima thickness at 1 year follow up in BRS (correlation coefficient range: -0.140 to -0.662).
Bourantas et al. (2015) <sup>56</sup>	43	13	Angiography, IVUS	ESS determines neointimal formation in both BMS (p < 0.001) and BES (p=0.002) and is a predictor of an increased necrotic core component in BMS.
Shishido et al. (2016) <sup>57</sup>	374	6-10	Angiography, IVUS	Low ESS after BMS implantation is associated with in stent hyperplasia. Post PCI ESS is not associated with in stent restenosis requiring repeat PCI.

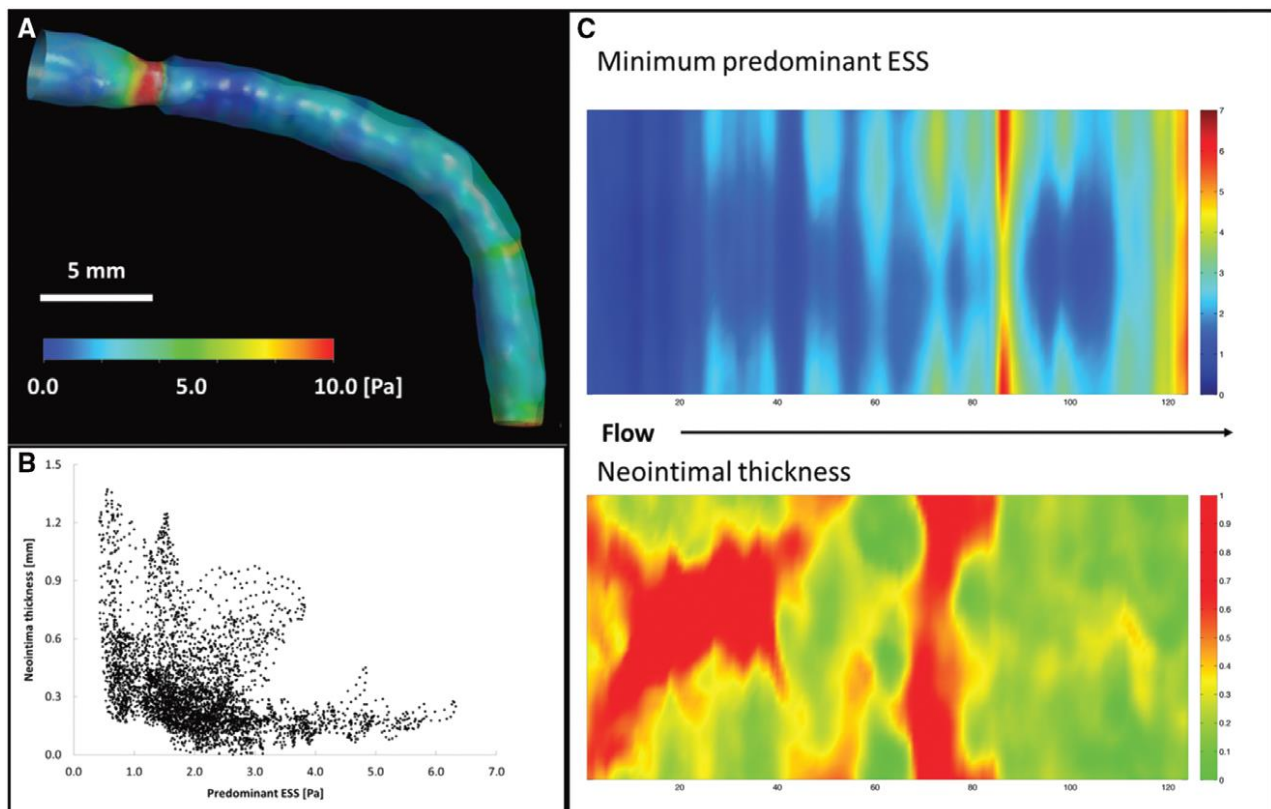
A summary on patient studies that look the effect of shear stress on atherosclerosis and restenosis. Most atherosclerosis showed an inverse association between ESS and plaque or neointima burden. BES indicates biolimus eluting stents; BMS, bare metal stents; BRS, bioresorbable scaffolds; ESS, endothelial shear stress; IVUS, intravascular ultrasound; OCT, optical coherence tomography; and PCI, percutaneous coronary intervention.



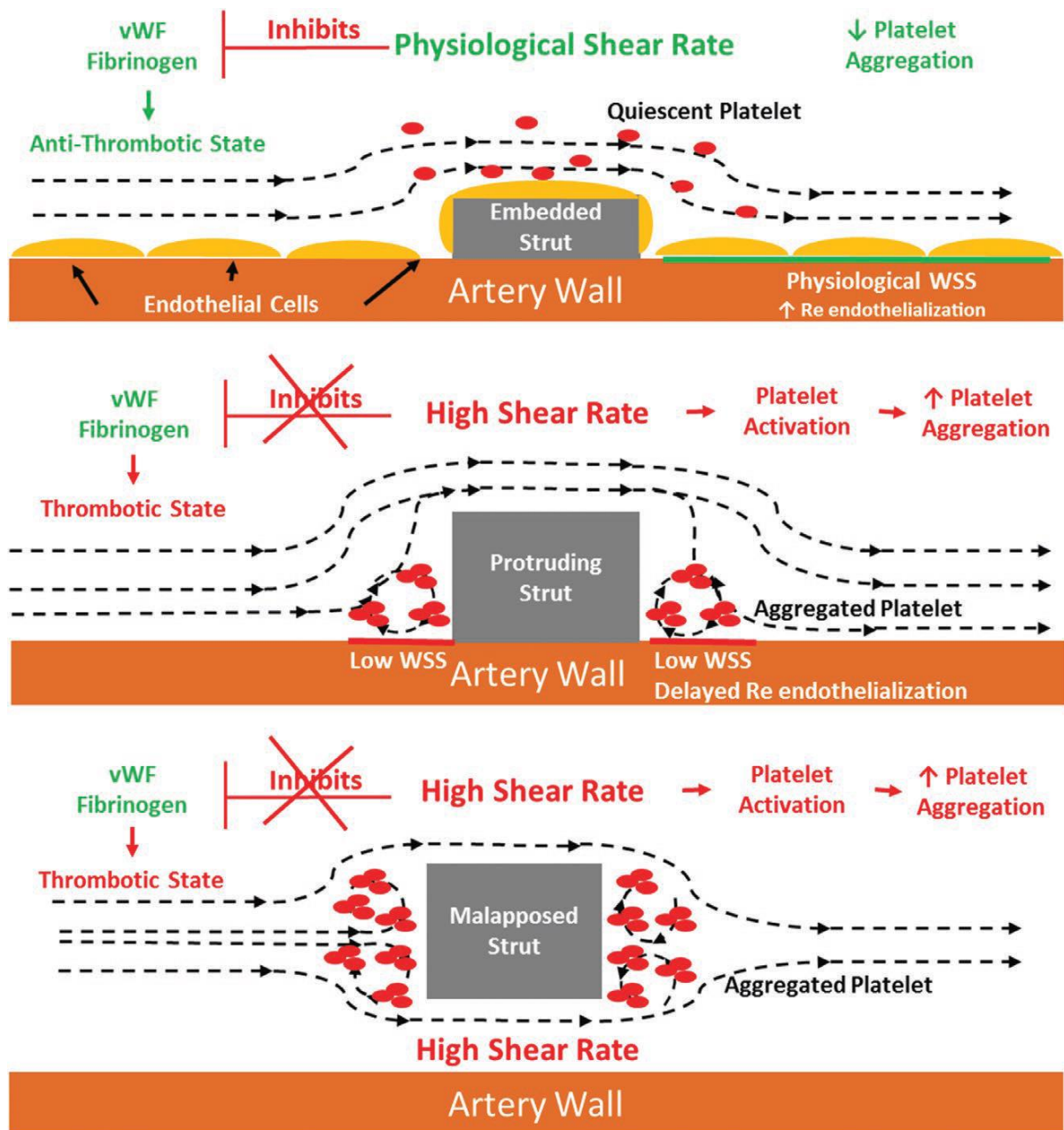
**Figure 1.** Optical coherence tomography (OCT)–based reconstruction and blood flow simulation immediately after scaffold implantation. This is an example of the use of high-resolution imaging modalities for the prediction of local hemodynamics and endothelial shear stress (ESS) after Absorb bioresorbable vascular scaffold (BVS) implantation. A magnified view of the OCT-derived lumen surface (A), revealing the strut architecture in the OCT-derived lumen surface (B). Protruding struts affect the local ESS distribution with higher values noted on top of the struts and lower values in the interstrut areas (B). Flow streamlines in a longitudinal cross-section (C); flow disturbance and recirculation regions around the struts regions (arrow and dotted arrow). Corresponding OCT cross-sectional images (evident by the side branch [br]) at baseline (D), ESS distribution (E), and 2-y follow-up (F). Intravascular ultrasound (IVUS)–based reconstruction of the scaffolded segment at baseline with the ESS shown in a color-coded map (G). IVUS cross-sectional images at baseline (H) and 2-y followup (J) corresponding to the OCT images. The lower IVUS resolution allows a rough assessment of BVS struts (\*) and cannot detect the neointima tissue. Note the smoother ESS distribution compared with the OCT-based model. A stronger correlation was noted between the baseline ESS and neointima thickness at 2 y in the OCT-based model (K,  $R^2=0.50$ ) compared with the IVUS-based reconstruction (L,  $R^2=0.13$ ). Reprinted from Papafakis et al<sup>3</sup> with permission. Copyright ©2013, Europa Digital & Publishing. 3D indicates 3-dimensional.



**Figure 2.** Shear rate and endothelial shear stress (ESS) definition. Shear rate is the velocity gradient along the diameter of the vessel. ESS is derived from the velocity gradient near the wall (shear rate) multiplied by the viscosity of the blood ( $\mu$ ). It has the dimension of force per unit area and is expressed generally in Pascal or dyne/cm<sup>2</sup> (1 Pa=10 dyne/cm<sup>2</sup>). In a straight cylindrical vessel of a radius  $r$  with a developed parabolic laminar flow profile (Poiseuille flow), ESS can be evaluated from the Hagen–Poiseuille equation:  $ESS=4Q\cdot\mu/(\pi r^3)$ , where  $Q$  is the flow-rate,  $\mu$  the fluid viscosity,  $r$  the tube radius. Adapted from Foin et al<sup>5</sup> with permission. Copyright ©2017.

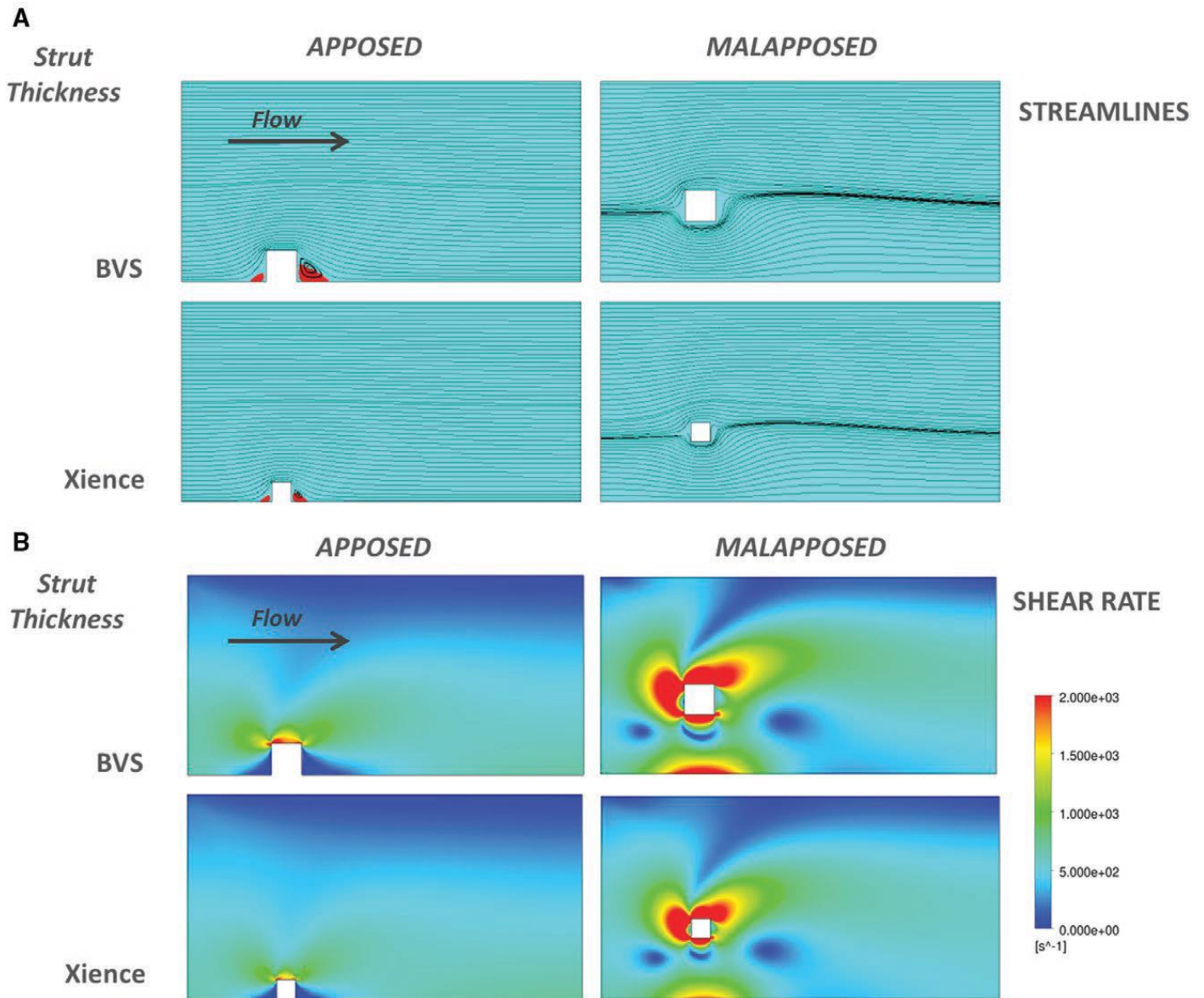


**Figure 3.** Correlation between baseline endothelial share stress (ESS) and thickness of neointima in a patient with 3.7 y of follow-up after stent implantation. **A**, ESS map on the baseline 3-dimensional vascular model (transparent) and vessel anatomy at the follow-up (gray surface inside). **B**, Point-to-point association between the baseline ESS and neointimal thickness within the stented segment, showing inverse-proportional correlation. **C**, Spread-out plots of ESS (**top**) and neointimal thickness (**bottom**) in the stented segment, demonstrating spatial relationship between low ESS and neointimal thickening.



**Figure 4.** Stent strut protrusion and thrombosis. Embedded struts disrupt blood flow the least out of the 3 scenarios and has the lowest area of recirculation and physiological levels of shear rate. Hence, activator proteins like vWF (Von Willebrand factor) are not activated, and platelet adhesion and aggregation remain at a minimum. Malapposed struts have regions of high shear rate both at the top and bottom of the strut and a larger surface area for adhesion proteins to bind to, creating a thrombogenic surface as compared with a protruding strut. At high shear rates, platelets are activated via the vWF binding to glycoprotein (GP) Ib and GP IIb/IIIa receptors<sup>13,108</sup> resulting in clot formation and potentially thrombosis formation.<sup>6,7</sup> Top panels adapted from Koskinas et al<sup>13</sup> with permission. Copyright ©2012, Elsevier.





**Figure 5.** Impact of strut thickness on blood flow profiles for model simulating case of well-apposed and malapposed drug-eluting stents (DES) and bioresorbable scaffolds (BRS) struts. **A**, Simulated blood flow streamlines (**top**) for the different cases of strut apposition: (1) apposed and (2) malapposed (with strut to wall distance=300  $\mu\text{m}$ ). Models are representative of a 3-mm diameter straight coronary artery flow with a parabolic upstream velocity profile and a peak velocity of 50 cm/s. The 2 strut thicknesses are considered to correspond to a total strut thickness (strut+coating) of 156  $\mu\text{m}$  (Absorb BVS) and 97  $\mu\text{m}$  (Xience DES). **B**, Corresponding shear rate profile in blood around stent strut simulated for each case (**bottom**) shows that flow disturbances and high shear rates (red) are increased primarily in thicker and malapposed struts. Reprinted from Foin et al99 with permission. Copyright ©2015, Europa Digital & Publishing.